Published in final edited form as:

J Neuroophthalmol. 2011 December ; 31(4): 362–373. doi:10.1097/WNO.0b013e318238937f.

Vision in Multiple Sclerosis (MS): The Story, Structure-Function Correlations, and Models for Neuroprotection

Reiko E. Sakai, BA, Daniel J. Feller, Kristin M. Galetta, MS, Steven L. Galetta, MD, and Laura J. Balcer, MD, MSCE

Departments of Neurology (RES, DJF, KMG, SLG, LJB), Ophthalmology (SLG, LJB) and Epidemiology (LJB), University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Abstract

Visual dysfunction is one of the most common clinical manifestations of multiple sclerosis (MS). Just over a decade ago, MS clinical trials did not include visual outcomes but experts recognized the need for more sensitive measures of visual function. Low-contrast letter acuity emerged as the leading candidate to measure visual disability in MS and subsequent studies found low-contrast acuity testing to correlate well with brain MRI lesion burden, visual-evoked potentials (VEPs), quality of life (QOL), and retinal nerve fiber layer (RNFL) loss as measured by optical coherence tomography (OCT). OCT in MS has allowed for assessment of structure-function correlations that make the anterior visual pathway and acute optic neuritis (ON) ideal models for testing novel agents for neuroprotection and repair. New therapies that reduce axonal loss by neuroprotective or myelin repair mechanisms can now be assessed non-invasively by OCT and coupled with visual function data. Based on OCT studies in MS, RNFL thickness is reduced significantly among patients (92 μm) versus controls (105 μm), and is particularly reduced in MS eyes with a history of ON (85 μm). Worsening of visual function by a clinically significant 7 letters or ~ 1.5 lines for low-contrast acuity is associated with approximately 4.5 μm reductions in RNFL thickness in MS eyes. Longitudinal studies of OCT have also shown RNFL axonal loss over time that occurs even in the absence of acute ON, and that correlates with clinically meaningful worsening of vision and QOL, even in patients with benign MS. The latest OCT investigations involve high-resolution spectral-domain (SD) OCT with segmentation and measurement of specific retinal layers using computerized algorithms. These methods allow quantitation of ganglion cell (neuronal) layer loss as well as axonal degeneration in MS *in vivo*. In this review, we examine the data from these studies and ongoing trials that highlight the entity of ON as a model to investigate neuroprotection and neurorepair. In doing so, we also present representative group data from studies that have examined visual function, OCT measures, and QOL scales in patients with MS, ON, and disease-free controls. These data, as well as those from recent meta-analyses, may be used to provide reference values for the development of clinical trial protocols.

Address correspondence to: Laura J. Balcer, MD, MSCE, 3 East Gates Building, Neurology, 3400 Spruce Street, Philadelphia, PA 19104, USA, 215-349-8072, Fax 215-662-3362, lbalcer@mail.med.upenn.edu, laura.balcer@uphs.upenn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: Dr. Galetta has received speaking and consulting honoraria from Biogen-Idec, Novartis, and Teva. Dr. Balcer has received speaking and consulting honoraria from Biogen-Idec, Bayer, and Novartis.

Keywords

multiple sclerosis (MS); visual pathway; low-contrast letter acuity; optical coherence tomography (OCT); neuroprotection

Visual loss has been recognized for decades as one of the most common and disabling clinical manifestations of multiple sclerosis (MS). It was not until a decade ago, however, that MS clinical trials began to include sensitive measures of visual function. Inspired by the effective use of contrast sensitivity (Pelli-Robson charts) to demonstrate visual abnormalities in the Optic Neuritis Treatment Trial (ONTT) (1–6), low-contrast letter acuity was introduced into MS trials as an exploratory outcome to better capture the often subtle visual symptoms experienced by patients with acute optic neuritis (ON) (7–10).

Visual symptoms can result from a variety of pathological processes, including inflammation, demyelination, and axonal degeneration in the afferent visual pathway, (retina, optic nerves, chiasm, and tracts) (11–15). During the past decade, the contributions of axonal and neuronal loss to disability in MS have been increasingly recognized (12, 16–19). Developed initially as a non-invasive tool to monitor retinal disease and glaucoma, optical coherence tomography (OCT) was first applied to cohorts of patients with MS and ON over a decade ago to provide validation of clinical visual outcomes and to capture anterior visual pathway axonal loss (15, 20–25). As a result of these early studies and >100 subsequent published investigations of OCT in MS and ON (26), the visual pathway is now recognized as a model for structure-function correlation in MS for studying the pathophysiology of disease and for testing both novel and standard therapies that involve neuroprotection and repair. OCT can be used non-invasively to capture reductions in axonal loss that may be associated with neuroprotective or myelin repair therapies; this information can be correlated with visual function and QOL data to further establish the clinical relevance of these structural outcomes.

OCT enables investigators to rapidly and reproducibly evaluate the structural composition of the retina. Ultimately, OCT could substantially increase our understanding of the mechanisms of tissue injury in MS, ON and other optic neuropathies.

A decade after publication of the first studies of low-contrast acuity in MS, this test as well as OCT measures are commonly used in MS clinical trials. They have formed the foundation for new trials that use acute ON as a model for identifying novel compounds for neurorepair (27–32).

This review describes a number of advancements in the development of visual function outcomes in MS as well as OCT as a novel technology that enables objective analysis of the processes of neurodegeneration. In addition, we present representative group data from studies that have examined visual function, OCT measures, and QOL scales in patients with MS, ON, and disease-free controls (Table 1). These data may be used to provide initial reference values and should be viewed in the context of 1) the continually-evolving field of vision in MS; 2) the potential challenge inherent in applying group data to individual patients; and 3) the perspective that even the small observed differences in mean OCT values have been shown to correlate with clinically meaningful changes in visual function and QOL in MS patients.

VISION IN MS: THE STORY

In the late 1990's, the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force developed the MS Functional Composite (MSFC) in response to the need for

more sensitive neurologic outcome scale (33, 34). Designed to be a battery of performance measures complementary to the Expanded Disability Status Scale (EDSS), the MSFC includes the 25-Foot Timed Walk, the 9-Hole Peg Test, and Paced Auditory Serial Addition Test (PASAT) (35–38). While multidimensional, the MSFC did not include a measure of visual function. In the evaluation of candidate MSFC visual components from MS clinical trial data used to develop the MSFC, Snellen high-contrast visual acuity (VA) did not change over time or demonstrate concurrent changes with EDSS scores (33). Contrast sensitivity, as tested by line gratings and letter charts in MS and by Pelli-Robson charts in the Optic Neuritis Treatment Trial (ONTT), had been shown to be a sensitive measure of afferent visual function, even among patient with Snellen acuities of 20/20 or better (1–6, 39–43). Importantly, measures of low-contrast vision are predictive of “real-world” visual tasks such as reading rate, facial recognition, and driving (44).

Low-Contrast Letter Acuity

While used successfully in the ONTT to demonstrate persistent visual abnormalities beyond recovery of high-contrast visual acuity, Pelli-Robson contrast sensitivity charts were not available for purchase in 1998 when the first MS clinical trial to incorporate a low-contrast visual measure as an exploratory outcome was begun. This trial, IMPACT (International MS Progressive Avonex Clinical Trial), incorporated low-contrast Sloan letter charts (7, 8, 45, 46). These charts are the low-contrast (gray letters on white) “cousin” of the ETDRS high-contrast VA charts used in ophthalmology clinical trials (Fig. 1). Sloan charts have a standardized format based on the ETDRS VA charts. Three contrast levels have been used in MS trials and research studies, including 100% (high-contrast, used to measure VA as a descriptor of the study cohorts), 2.5%, and 1.25% (lightest contrast level). Charts are scored letter by letter, and numbers of letters identified correctly constitute the score for each chart (Table 1). Most recently, visual improvement and loss by the low-contrast acuity chart has been defined as a 7-letter change in score, while 5-letter changes in high-contrast VA are now considered clinically significant for patients with good visual acuity (47). This threshold represents a change that exceeds that which would be expected from repeated testing when there was no real change (45, 48), and to correlate with RNFL axonal loss in patients with MS (47). As shown in Table 1, differences in mean letter scores for MS vs. disease-free control groups are consistently 5 letters for VA and 7 letters for low-contrast acuity. Since the 5- and 7-letter criteria are meant to be applied to individual eye or patient differences, differences in mean scores of such magnitude are therefore likely to be clinically meaningful. Furthermore, these 5- and 7-letter mean changes have been shown to correlate significantly with vision-specific and overall QOL as well as structural measures of OCT RNFL thickness. These associations of OCT and QOL measures with clinically meaningful changes in visual function provide perspective for the data in Table 1 despite the seemingly small magnitudes of differences in means for OCT values.

In the IMPACT trial and in heterogeneous MS cohorts (7, 8, 45), low-contrast letter acuity was shown to be a highly reliable (high intraclass correlations of 0.86–0.95) and practical method that was superior in identifying MS-related visual loss compared to other available tests (Fig. 2). Correlations of Sloan chart scores with MS Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS) in these studies were significant and moderate in magnitude ($r_s=0.56$ vs. MSFC; $r_s=-0.43$ vs. EDSS, $P<0.0001$). These studies provided the first ever data demonstrating that low-contrast acuity scores capture unique aspects of dysfunction not captured by standard neurologic scales of EDSS or the MSFC, and suggested that adding a visual component to the MSFC would increase the applicability of this measure.

In the AFFIRM trial of natalizumab vs. placebo for relapsing-remitting MS, low-contrast letter acuity was able to demonstrate treatment effects and changes over time both with

respect to reduction of the cumulative probability of sustained visual loss (by 47%, $P<0.001$ for 2.5% contrast level) and sustained clinically meaningful visual improvement (by 57%, $P=0.01$) in the treatment group (9, 10). Similar to previous studies and to MS trial datasets used originally to develop the MSFC, high-contrast VA did not show treatment differences or detect sustained visual loss or improvement over time. The analyses of visual loss in AFFIRM used initially a 2-line (10-letter) criterion for clinically significant change; subsequent ophthalmologic studies for VA, however, suggested use of a one-line (5-letter cutoff). Examination of inter-rater and test-retest reliability data for low-contrast acuity revealed 7 letters to represent 2 standard deviations on the inter-rater differences; this 7-letter criterion was subsequently incorporated into the AFFIRM analyses of visual improvement as well as subsequent longitudinal studies of optical coherence tomography (OCT).

Vision-Specific Quality of Life (QOL) Measures

The relevance of low-contrast letter acuity measurements to patient functioning has been underscored by studies linking these scores to vision-specific quality of life (QOL). Scores for the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) are reduced among patients with MS (Table 1) (49–51). A 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 has also been designed using MS cohorts to capture symptoms relevant to neurologic disease. In a recent study of 167 patients with MS, two-line differences in visual function by low-contrast acuity are associated, on average, with >4-point (6.7 – 10.9-points, $P<0.001$ accounting for age) worsening in NEI-VFQ-25 composite (overall) score, reductions that are considered to be clinically meaningful based on ophthalmic epidemiologic studies (52–55). In Table 1, the differences in mean scores between MS patients and disease-free controls were 4 points; such differences may be considered clinically significant for both individual changes and group data. Binocular scores for low-contrast acuity also correlated significantly with score for the 10-Item Neuro-Ophthalmic Supplement ($P<0.001$), the Impact of Visual Impairment Scale (IVIS, $P<0.001$) and the SF-36 Physical Components Summary ($P<0.001$) in this MS cohort. Collectively, these data demonstrated that low-contrast acuity testing provides information on patient-reported aspects of vision. This is a key feature for clinical measures and a prerequisite for their use as primary outcomes in clinical trials.

Binocular Summation of Acuity

While the earliest studies of low-contrast acuity and QOL examined binocular vision scores (vision testing with both eyes together), monocular measurements (with each eye separately) have more recently been introduced into MS trials and vision research with the inclusion of optical coherence tomography (OCT) scanning as a structural correlate to vision (Table 1). Given the importance of both of these types of acuity to measurements of function, analyses of MS cohort data including both binocular and monocular scores were undertaken to examine the relation between the two and to determine the potential roles for binocular summation and inhibition (56). Binocular summation of acuity occurs when vision is improved under binocular viewing conditions (binocular score is greater than the scores for either eye alone) (57). In contrast, patients with binocular inhibition have worse binocular vision compared to the better eye alone. Among 1,007 patients with MS and 324 disease-free controls, binocular summation was substantial (5–7-letter increases over better eye acuity, 28–52% with >7 letters, $P<0.001$) for low-contrast acuity at the 2.5% and 1.25% levels. For high-contrast VA, only 3.0–3.4% of patients showed similar degrees of summation. Increasing age ($P<0.0001$), greater interocular differences in acuity ($P<0.0001$), and prior history of ON ($P=0.015$) were associated with lower magnitudes of binocular summation; in fact, some of these patients had binocular inhibition. Importantly, greater degrees of binocular summation were predictive of better QOL by the NEI-VFQ-25

($P=0.02$) and 10-Item Supplement ($P=0.03$), indicating that the capacity to use both eyes together is an important factor in determining how well patients with MS can perform daily activities (56).

Relation of Vision to MRI and Visual Evoked Potentials

Correlation with biological markers as well as electrophysiological measures of disease is one of the most important factors in the evaluation of clinical outcome measures such as low-contrast letter acuity. The first such study determined the relation of binocular low-contrast scores to brain MRI measures of T2 lesion burden (58). This study of 45 patients with MS found that those with worse low-contrast acuity scores had greater T2 lesion volumes in whole brain (3 mm^3 increase for every 1-line worsening, $P=0.002-0.004$, accounting for age and disease duration). Area 17 and optic radiation white matter lesion burden specifically correlated with visual function, but non-vision-related white matter did not show associations. These findings were important in providing a structural correlate to low-contrast acuity scores, and also in emphasizing a potential post-geniculate pathway component to binocular low-contrast vision.

Standard brain MRI techniques have provided information regarding disease burden in MS. However, the capacity for these techniques to precisely quantify axonal and neuronal loss, particularly in the anterior visual pathway, has been limited. Electrophysiologic markers such as the visual-evoked potential (VEP) can provide additional information on anterior visual pathway integrity. Recent studies have combined assessments of vision loss with VEP. Conventional VEPs measure the cortical response to monocular stimulation in the central 30 degrees of the visual field. In MS, the latency characteristically is delayed with normal amplitude. Axonal loss, however, can reduce this amplitude (59). Abnormal VEPs in unaffected eyes provided evidence for clinically silent lesions in the optic nerve that might help identify dissemination in space and help establish the diagnosis of MS (60). Various studies have shown that contrast sensitivity can be measured by VEP (43), and VEP in MS using low-contrast stimuli show increased latencies or absent waveforms when compared with high-contrast stimuli VEPs. Low-contrast VEP may prove to be helpful in identifying demyelination (61). Other studies have concluded that multifocal VEP provides higher sensitivity and specificity in detecting abnormalities in visual function in MS and in ON (62).

Naismith et al. (63) systematically evaluated the utility of OCT and VEPs to detect the presence of clinical and subclinical ON, and examined the relation of these measures to visual function. This retrospective, cross-sectional study evaluated 65 subjects ($n=96$ eyes) with MS ($n=40$), clinically isolated syndrome (CIS, $n=1$), neuromyelitis optica (NMO, $n=20$) and idiopathic demyelination ($n=4$). Patients had at least one episode of ON 6 months prior to enrollment. VEPs detected ON in 81% of patients (32% of subclinical ON in unaffected eyes and 75% of all subclinical ON). In contrast, using their criteria, they found that OCT identified 60% of eyes with ON, and less than 20% of subclinically affected eyes. The authors concluded that OCT is less sensitive than VEPs in optic neuritis. On the other hand, to the extent that this study focused on patients with relatively poor vision, there were likely floor effects with regard to OCT RNFL thickness.

STRUCTURE-FUNCTION CORRELATIONS: OCT

Although acute ON and demyelination are important contributors to visual dysfunction, irreversible axonal and neuronal degeneration are also final common pathways to permanent visual loss (12–14, 24, 64). While the relationship between visual loss and brain MRI lesion burden discussed above is a relatively new finding, the extremely high predilection for MS to involve the optic nerves is well-documented and was initially observed long before the

advent of advanced optical and neuroimaging. Autopsy studies have shown that up to 94–99% of MS patients have detectable optic nerve lesions (65, 66). Sub-clinical changes related to visual loss may involve the optic nerves or chiasm, or post-chiasmal regions of the optic tract (13, 67–69).

Features and Advantages of OCT Imaging

OCT provides a non-invasive technique to measure axonal and neuronal loss in the anterior visual pathways (24, 28–32). As the optical analog of ultrasound B-mode imaging, OCT allows us to image the retinal nerve fiber layer (RNFL) (15, 20–32, 47, 59, 70–82). Since, within the retina, these axons are non-myelinated, the RNFL is an ideal structure with which to visualize the processes of neurodegeneration, neuroprotection, and potentially even neuro-repair. In contrast to the peripapillary RNFL, which contains axons, the macula contains a large proportion of retinal ganglion cell neurons (about 34% of total macular volume) (81). The development of Fourier-domain (or spectral-domain [SD]) detection has in particular enhanced ophthalmic OCT technology. While many of the studies cited in this review utilized time-domain (TD) OCT, some have incorporated the newer SD OCT technologies. Table 1 presents some representative group data for OCT measures in patients with MS, ON, and disease-free controls. Since OCT measures have been shown to correlate with clinically meaningful changes in visual function and QOL (see above), the differences in mean values between groups shown in Table 1 are likely to have clinical significance. Larger studies and additional meta-analyses will allow us to further refine the precision of these representative average values.

OCT Investigations in MS and ON

The earliest application of OCT technology to the study of MS was reported by Parisi et al. in 1999 (15). In this study, which utilized first-generation OCT technology, 14 patients with MS who had completely recovered from a previous event of acute optic neuritis (ON) were analyzed. The thickness of the RNFL was shown to be reduced by 46% in the affected eyes of the patients with MS versus the control eyes ($P<0.01$), and by 28% when affected eyes were compared with the ‘unaffected’ eyes of the same patient ($P<0.01$). Even in the clinically unaffected eyes of patients, however, there was a 26% reduction in RNFL thickness when compared with control eyes ($P<0.01$).

In 2005, Trip and colleagues (21) reported their observations with OCT in 11 patients with MS and 14 patients with clinically isolated syndrome (CIS), all of which individuals had a history of a single episode of ON. The study was a cross-sectional analysis with follow-up ranging from 1 to 9 years after the optic neuritis event. Corroborating the previous findings by Parisi et al. (15), the investigators found a 33% reduction in RNFL thickness in the eyes of the patients when compared with the eyes of matched controls, and a 27% reduction when the affected and unaffected eyes of the same patient were compared ($P<0.001$). Trip et al. (21) extended the utility of OCT by also showing that the macular volume (a reflection of retinal ganglion cell neuronal integrity) was reduced by 11% in the eyes of patients with a history of ON when compared with control eyes ($P<0.001$), and by 9% in the affected versus the unaffected eye of the same patient ($P<0.001$).

In 2006, Costello and colleagues (20) reported that the majority of patients with MS who have ON (about 75%) will sustain 10–40 μm of RNFL loss within a period of approximately 3–6 months. This finding is striking given that the RNFL is only about 110–120 μm thick by the age of 15 years, and that most individuals (without a history of glaucoma or macular degeneration) will lose only about 0.017% per year in retinal thickness, which equates to approximately 10–20 μm over 60 years (25, 83). Costello et al. (20) also provided compelling evidence identifying an injury threshold within the RNFL of about 75 μm ;

thinning of the RNFL below this level led to a corresponding decline in visual function, as measured by automated perimetry. Using low-contrast letter acuity in MS eyes with a history of acute ON, we have found a similar threshold for abnormal visual function and axonal loss at 80 μm (Fig. 3).

The trajectory and time course of RNFL axonal loss following an episode of acute ON is an important for determining the “window of opportunity” within which a neuroprotective or repair agent should be administered in a treatment trial. Sample size calculations for a proposed ON trial are also likely to be based on such data. Henderson et al. (84) recently addressed both of these questions in a study of 23 patients with acute clinically isolated unilateral ON. Patients underwent time-domain (TD) OCT assessment of RNFL thickness and total macular volume; visual function testing with high-contrast VA, low-contrast acuity (Sloan charts at 1.25%), Farnsworth-Munsell 100 color testing, and automated visual fields; and pattern VEP testing. The mean time to 90% loss from the initial RNFL thickness values for affected eyes (initial median 116.5 μm ---likely reflecting slight edema) was 2.38 months (95% CI 1.95, 2.77; $P<0.05$). Ninety-nine percent of the loss from the initial value to the asymptotic value (lowest point where loss leveled off) occurred by a mean of 4.75 months (95% CI 3.90, 5.54; $P<0.05$). The time of first detectable RNFL atrophy compared to the baseline fellow eye value was 1.64 months (95% CI 0.96, 2.32; $P<0.05$). Eyes with poor recovery ($n=5$), defined as logMAR VA >0.1 , had a significantly greater decline of RNFL from baseline to 3 months ($P=0.002$). Macular volumes also declined significantly to the time of last follow-up. Sample size estimates using their models showed that, assuming 80% power, approximately 100–150 patients would be needed to detect a 30% decrease in RNFL loss between the treatment and placebo groups at a 3–6 month endpoint. These findings are critical in setting the stage for use of acute ON as a model for neuroprotection and repair trials (84).

One of the most important findings that has resulted from the use of OCT MS studies is the correlation between RNFL thinning and visual loss, as measured by low-contrast letter acuity. In 2005, Fisher et al. (22) conducted a cross-sectional study that compared RNFL thickness among MS eyes with a history of ON (MS ON eyes), MS eyes without a history of ON (MS non-ON eyes) and disease-free controls. In addition to OCT measurement of OCT, they conducted low-contrast visual assessments with low-contrast letter acuity, contrast sensitivity (Pelli-Robson charts), high contrast VA (ETDRS charts). The authors found that RNFL thickness was reduced significantly among MS patients (92 μm) versus controls (105 μm , $P<0.001$), and particularly reduced in MS ON eyes (85 μm , $P<0.001$). Furthermore, lower visual function scores were associated with reduced average overall RNFL thickness in MS eyes; for every 1-line decrease in low-contrast letter acuity or contrast sensitivity score, the mean RNFL thickness decreased by 4 μm . These findings not only supported the validity of low-contrast visual assessment as a secondary clinical outcome measure in MS trials, they also suggested a potential role for OCT in trials that examine neuroprotective and other disease-modifying therapies. Several other investigations have demonstrated correlations between RNFL thinning and visual loss (21, 25, 77, 85–87).

While the above studies used cross-sectional studies to examine relationships between biomarkers measured with OCT and visual function, the first longitudinal study to study the relationship between RNFL thickness and visual loss was carried out by Talman et al in 2010 (47). These investigators used OCT to measure RNFL thickness at baseline and at 6-month intervals during a mean follow-up of 18 months at 3 centers. Low-contrast letter acuity (2.5% and 1.25%) and high contrast visual acuity (VA) were tested. The results indicated that among 299 patients (593 eyes) with at least 6 month follow-up, eyes with visual loss showed greater RNFL thinning compared to eyes with stable vision (low-contrast acuity, 2.5%: $P<0.001$; VA: $P=0.005$). RNFL thinning increased over time, with average

losses of 2.9 μm at 2 to 3 years and 6.1 μm at 3–4.5 years ($P<0.001$ vs. 0.5–1 year follow-up). The authors concluded that progressive RNFL thinning occurs as a function of time in some patients with MS, even in the absence of ON (47). Studies such as this draw the important connection between structure (RNFL thickness and macular volume, as measured by OCT) and function (visual performance as measured by low-contrast acuity), and are likely to be instrumental in improving our understanding of the MS disease process.

Recently, OCT has also been used to show the capacity of RNFL thinning to distinguish MS disease subtypes. Costello and colleagues (85) found that RNFL comparisons involving eyes without ON yielded greater differences between MS subtypes than ON-affected eyes. Overall RNFL values in non-affected eyes were reduced in Secondary Progressive MS patients (SPMS) (83.4 μm), relative to ON as a clinically isolated syndrome (CIS) (101.2 μm) ($P=0.0009$), and relapsing-remitting MS (RRMS) patients (103.7 μm) ($P=0.001$); and temporal RNFL atrophy was greater in RRMS (64.4 μm) eyes as compared to CIS eyes (73.2 μm , $P=0.02$). In ON-affected eyes, RNFL atrophy was greater in SPMS patients (39.5 μm) than CIS patients (58.1 μm , $P=0.03$), and in RRMS patients (48.2 μm) relative to CIS patients ($P=0.05$). These authors concluded that RNFL thickness might represent an important MS structural marker because RNFL thinning reflects disease progression.

While RNFL thinning is most marked in patients with SPMS, those with benign MS, traditionally defined as EDSS ≤ 3 and ≤ 15 years disease duration, are thought to follow a milder course (88). We recently conducted an analysis of a longitudinal MS cohort to determine the extent of visual pathway axonal loss by OCT RNFL thickness. At three academic centers, a subset of patients with EDSS scores, visual function, OCT, and QOL assessments was analyzed. Low- and high-contrast letter acuity were performed to assess visual function. RNFL thickness was determined using OCT-3. QOL scales included the NEI-VFQ-25 and SF-36. Among 68 patients (135 eyes) studied longitudinally, 13 (26 eyes) had benign MS using criteria of EDSS ≤ 3 and ≤ 15 years disease duration. Benign MS eyes had as much RNFL thinning ($-3.6 \mu\text{m}$, $P=0.0008$ vs. baseline, paired t-test) as typical MS eyes ($-3.3 \mu\text{m}$, $P<0.0001$). Both groups had significant low-contrast acuity loss over time. Prior history of optic neuritis (ON) was more frequent in benign MS (69% vs. 33% of eyes). History of ON distinguished benign vs. typical MS ($P=0.002$) and correlated with RNFL thickness at baseline ($P=0.002$) and disease duration ($P=0.03$), but not EDSS ($P=0.32$, logistic regression). NEI-VFQ-25 scores were also worse for benign MS, accounting for age (75 ± 21 vs. 88 ± 11 , $P=0.005$). These findings demonstrated that patients with benign MS have RNFL axonal loss that is as marked as that of typical MS, and have reduced vision and QOL. While overall neurologic impairment is mild, visual dysfunction, not well-captured by the EDSS, accounts for a substantial degree of disability in benign MS.

The Future of OCT in MS: Retinal Segmentation

In addition to axonal degeneration, neuronal loss is increasingly recognized as a correlate of disability in MS (16–19, 89–91). While investigations of time-domain OCT have shown reductions in total macular volume as a potential marker for neuronal loss in MS eyes, more specific measurement of the retinal ganglion cell layer (GCL) and other layers by segmentation has only recently emerged following the introduction of high-resolution and high-speed -domain (SD) OCT techniques to study of MS (Table 1) (25–27, 82, 92–100). Earlier studies of total macular volume using TD- OCT suggested that retinal ganglion cell neuronal loss occurs in MS eyes and that this correlates with visual function (81). These observations were necessarily based on the structural assumption that ~34% of the total macular volume is comprised of ganglion cells.

Using SD- OCT, some of the first observations of specific retinal ganglion cell layer (GCL) loss in MS eyes were generated by a study that involved manual delineation of the GCL on a

Spectralis OCT platform (Fig. 4) (97). In this pilot investigation, eyes of patients with MS (n=16) had significantly lower GCL volumes than control eyes ($P<0.001$, accounting for age and within-patient, inter-eye correlations). Lower volumes were noted among MS eyes with a prior history of ON (n=4) compared to MS non-ON eyes ($P<0.001$). Reduced GCL volumes were not associated with worse high-contrast VA ($P=0.14$), but did predict visual loss by low-contrast acuity ($P=0.003$).

While manual OCT retinal segmentation demonstrated important findings in these studies, the labor-intensive nature of this technique (~2 hours per eye) limits its large scale use in MS cohorts. Computerized segmentation algorithms have been used successfully in studies of glaucoma (99, 100) and have provided the basis for two recent investigations in MS cohorts. Saidha et al. (96) used a segmentation method developed commercially to study patients with a macular thinning predominant (MTP) MS phenotype. These patients have peripapillary RNFL thickness that is within the normal ranges, but exhibit severe <5th percentile thinning of the macular region on spectral-domain OCT. This group of patient eyes demonstrated thinning of the outer retinal layers ($P<0.001$ for inner and outer nuclear layers in MTP vs. MS eyes), with relative sparing of the GCL. Patients with the MTP phenotype also had relatively greater degrees of overall neurologic disability, suggesting that these individuals may have a distinct or primary process underlying their neuronal loss.

Recent pathologic studies of post-mortem eyes from heterogeneous MS cohorts (n=82) demonstrated that the GCL is a site of neuronal dropout in 79% of eyes (101). Retinal ganglion cell loss has also been shown to occur *in vivo* in mouse models of relapsing-remitting experimental autoimmune encephalomyelitis (EAE) with optic nerve involvement, and to be reduced by neuroprotective therapies such as resveratrol in these models (102). To examine GCL loss in MS *in vivo* in patients with MS, our collaborative MS vision research group has used a novel computerized segmentation algorithm developed at the University of Pittsburgh (103). In this study, patients with MS (n=122 subjects, 239 eyes) and disease-free controls (n=31 subjects, 61 eyes) underwent Cirrus SD-OCT (Carl Zeiss-Meditec, Dublin, CA). Images were captured using Macular Cube (200×200 or 512×128) and ONH Cube 200×200 scanning protocols. Retinal layer segmentation was performed using algorithms originally designed for studies of glaucoma. Thicknesses of the ganglion cell layer/inner plexiform layer (GCL+IPL), RNFL, outer plexiform/inner nuclear layer (OPL+INL), and outer nuclear/photoreceptor layer (ONL+PRL) were measured and compared in MS vs. control eyes as well as MS ON vs. non-ON eyes. Since the IPL is a thin layer that is currently inseparable from the GCL using OCT, the combination GCL+IPL is used to estimate GCL thickness. Macular RNFL and GCL+IPL were significantly decreased in MS subjects vs. controls ($P<0.001$, $P=0.001$) and in MS ON eyes vs. non-ON eyes ($P<0.001$ for both measures). Peripapillary RNFL, macular RNFL, and GCL+IPL were all significantly correlated with VA ($P=0.001$), 2.5% low-contrast acuity ($P<0.001$), and 1.25% low-contrast ($P=0.001$). Among OCT measurements, reductions in GCL+IPL ($P<0.001$) and macular RNFL ($P=0.006$) were the most strongly associated with lower (worse) NEI-VFQ-25 and 10-Item Supplement composite scores for QOL; GCL+IPL thinning was significant even accounting simultaneously for macular RNFL thickness ($P=0.03$ for GCL+IPL and $P=0.39$ for macular RNFL). These data demonstrate that GCL+IPL thinning is most significantly correlated with both visual function and vision-specific QOL in MS. GCL thickness is likely to emerge as a useful structural marker of disease. These findings parallel those of MRI studies that show gray matter disease is a marker of neurologic disability in MS.

Vision and OCT in MS Clinical Trials: Role for Reading Centers

The incorporation of OCT and visual outcome measures into MS clinical trials has benefited from the presence of OCT reading centers. The University of California (UC) Davis Reading Center recently published the results of Stratus (time-domain) OCT quality control

in two multi-center MS clinical trials (104). The authors evaluated 19,961 OCT scans from 981 patients with the goal of determining the influence of OCT quality control procedures on error rate. In Trial 1 (design and therapeutic agent not specified in publication), there was no ophthalmic technician certification and data were obtained by the Reading Center retrospectively. However, in Trial 2, technicians were certified and submitted data prospectively according to the study protocol. OCT scans in Trial 2 had higher signal strengths, fewer errors, and more usable data compared to Trial 1 scans. This study showed that certified technicians and prompt transmission of data for ongoing quality control monitoring provide higher data quality; these factors and the use of Reading Centers should be considered in the design of clinical trials for MS and other neuro-ophthalmologic disorders.

CONCLUSIONS

Visual dysfunction is not only an important contributor to impairment and disability in MS, but represents a unique opportunity for studying disease mechanisms and for testing new therapies that involve neuroprotection and repair. The advent of ocular imaging with OCT has allowed investigators to examine *in vivo* the morphological changes that accompany visual loss. Sensitive visual function tests, including low-contrast letter acuity, have been shown to correlate with OCT measures of axonal and neuronal loss as well as with patient-reported assessments of QOL. These observations have been instrumental in the establishment of a structure-function paradigm for using the anterior visual pathway as a model in MS. Low-contrast letter acuity, vision-specific QOL measures (NEI-VFQ-25 and 10-Item Neuro-Ophthalmic Supplement), and OCT measures have been incorporated into recent MS clinical trials. It is likely that these emerging data will yield important findings for therapeutics in MS, ON, and other neuro-ophthalmologic causes of visual loss.

Acknowledgments

Funding for Studies of Vision and OCT in MS: National MS Society PP1115, RG 3208-A-1, RG 3428-A/2, National MS Society Translational Research Partnership TR 3760-A-3, NIH/ NEI K24 EY 014136, R01 EY 019473 (Dr. Balcer), McNeill Foundation, and DADs Foundation.

REFERENCES

1. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology*. 2008; 115:1079–1082. [PubMed: 17976727]
2. Beck RW, Gal RL, Bhatti MT, Brodsky MC, Buckley EG, Chrousos GA, Corbett J, Eggenberger E, Goodwin JA, Katz B, Kaufman DI, Keltner JL, Kupersmith MJ, Miller NR, Moke PS, Nazarian S, Orengo-Nania S, Savino PJ, Shults WT, Smith CH, Trobe JD, Wall M, Xing D. Optic Neuritis Study Group. Visual function more than 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Am J Ophthalmol*. 2004; 137:77–83. [PubMed: 14700647]
3. Cleary PA, Beck RW, Anderson MM Jr, Kenny DJ, Backlund JY, Gilbert PR. Design, methods, and conduct of the Optic Neuritis Treatment Trial. *Control Clin Trials*. 1993; 14:123–142. [PubMed: 8500302]
4. Trobe JD, Beck RW, Moke PS, Cleary PA. Contrast sensitivity and other vision tests in the optic neuritis treatment trial. *Am J Ophthalmol*. 1996; 121:547–553. [PubMed: 8610798]
5. Volpe NJ. The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. *Arch Ophthalmol*. 2008; 126:996–999. [PubMed: 18625952]
6. Keltner JL, Johnson CA, Cello KE, Dontchev M, Gal RL, Beck RW. Optic Neuritis Study Group. Visual field profile of optic neuritis: a final follow-up report from the optic neuritis treatment trial from baseline through 15 years. *Arch Ophthalmol*. 2010; 128:330–337. [PubMed: 20212204]

7. Balcer LJ, Baier ML, Cohen JA, Kooijmans MF, Sandroock AW, Nano-Schiavi ML, Pfohl DC, Mills M, Bowen J, Ford C, Heidenreich FR, Jacobs DA, Markowitz CE, Stuart WH, Ying GS, Galetta SL, Maguire MG, Cutter GR. Contrast letter acuity as a visual component for the Multiple Sclerosis Functional Composite. *Neurology*. 2003; 61:1367–1373. [PubMed: 14638957]
8. Baier ML, Cutter GR, Rudick RA, Miller D, Cohen JA, Weinstock-Guttman B, Mass M, Balcer LJ. Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. *Neurology*. 2005; 64:992–995. [PubMed: 15781814]
9. Balcer LJ, Galetta SL, Calabresi PA, Confavreux C, Giovannoni G, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Miller DH, O'Connor PW, Phillips JT, Polman CH, Radue EW, Rudick RA, Stuart WH, Wajgt A, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology*. 2007; 68:1299–1304. [PubMed: 17438220]
10. Balcer LJ, Galetta SL, Polman PH, Eggenberger E, Calabresi PA, Zhang A, Scanlon JV, Hyde R. Low-contrast acuity measures visual improvement in a phase 3 trial of natalizumab in relapsing MS. [unpublished data].
11. Graves J, Balcer LJ. Eye disorders in patients with multiple sclerosis: natural history and management. *Clin Ophthalmol*. 2010; 4:1409–1422. [PubMed: 21188152]
12. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med*. 1998; 338:278–285. [PubMed: 9445407]
13. Evangelou N, Konz D, Esiri MM, Smith S, Palace J, Matthews PM. Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. *Brain*. 2001; 124:1813–1820. [PubMed: 11522583]
14. DeLuca GC, Williams K, Evangelou N, Ebers GC, Esiri MM. The contribution of demyelination to axonal loss in multiple sclerosis. *Brain*. 2006; 129:1507–1516. [PubMed: 16597651]
15. Parisi V, Manni G, Spadaro M, Colacino G, Restuccia R, Marchi S, Bucci MG, Pierelli F. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. *Invest Ophthalmol Vis Sci*. 1999; 40:2520–2527. [PubMed: 10509645]
16. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray Matter Atrophy in Multiple Sclerosis: A Longitudinal Study. *Ann Neurol*. 2008; 64:255–265. [PubMed: 18661561]
17. Pirko I, Lucchinetti CF, Sriram S, Bakshi R. Gray matter involvement in multiple sclerosis. *Neurology*. 2007; 68:634–642. [PubMed: 17325269]
18. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkil KA, Thompson AJ, Miller DH. Gray matter atrophy is related to long-term disability in multiple sclerosis. *Ann Neurol*. 2008; 64:247–254. [PubMed: 18570297]
19. Chard D, Miller D. Grey matter pathology in clinically early multiple sclerosis: evidence from magnetic resonance imaging. *J Neurol Sci*. 2009; 282:5–11. [PubMed: 19201002]
20. Costello F, Coupland S, Hodge W, Lorello GR, Koroluk J, Pan YI, Freedman MS, Zackon DH, Kardon RH. Quantifying axonal loss after optic neuritis with optical coherence tomography. *Ann Neurol*. 2006; 59:963–969. [PubMed: 16718705]
21. Trip SA, Schlottmann PG, Jones SJ, Altmann DR, Garway-Heath DF, Thompson AJ, Plant GT, Miller DH. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. *Ann Neurol*. 2005; 58:383–391. [PubMed: 16075460]
22. Fisher JB, Jacobs DA, Markowitz CE, Galetta SL, Volpe NJ, Nano-Schiavi ML, Baier ML, Frohman EM, Winslow H, Frohman TC, Calabresi PA, Maguire MG, Cutter GR, Balcer LJ. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology*. 2006; 113:324–332. [PubMed: 16406539]
23. Frohman E, Costello F, Zivadinov R, Stuve O, Conger A, Winslow H, Trip A, Frohman T, Balcer L. Optical coherence tomography in multiple sclerosis. *Lancet Neurol*. 2006; 5:853–863. [PubMed: 16987732]
24. Frohman EM, Fujimoto JG, Frohman TC, Calabresi PA, Cutter G, Balcer LJ. Optical coherence tomography: a window into the mechanisms of multiple sclerosis. *Nat Clin Pract Neurol*. 2008; 4:664–665. [PubMed: 19043423]

25. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical coherence tomography (OCT): imaging the visual pathway as a model for neurodegeneration. *Neurotherapeutics*. 2011; 8:117–132. [PubMed: 21274691]
26. Petzold A, de Boer JF, Schippling S, Vermersch P, Kardon R, Green A, Calabresi PA, Polman C. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol*. 2010; 9:921–932. [PubMed: 20723847]
27. Barkhof F, Calabresi PA, Miller DH, Reingold SC. Imaging outcomes for neuroprotection and repair in multiple sclerosis trials. *Nat Rev Neurol*. 2009; 5:256–266. [PubMed: 19488083]
28. Jindahra P, Hedges TR, Mendoza-Santiesteban CE, Plant GT. Optical coherence tomography of the retina: applications in neurology. *Curr Opin Neurol*. 2010; 23:16–23. [PubMed: 20009925]
29. Lameril C, Newman N, Biousse V. The use of optical coherence tomography in neurology. *Rev Neurol Dis*. 2009; 6:E105–E120. [PubMed: 20065921]
30. Sakata LM, Deleon-Ortega J, Sakata V, Girkin CA. Optical coherence tomography of the retina and optic nerve - a review. *Clin Experiment Ophthalmol*. 2009; 37:90–99. [PubMed: 19338607]
31. Glisson CC, Galetta SL. Nonconventional optic nerve imaging in multiple sclerosis. *Neuroimag Clin N Am*. 2009; 19:71–79.
32. Kallenbach K, Frederiksen J. Optical coherence tomography in optic neuritis and multiple sclerosis: a review. *Eur J Neurol*. 2007; 14:841–849. [PubMed: 17662003]
33. Rudick R, Antel J, Confavreux C, Cutter G, Ellison G, Fischer J, Lublin F, Miller A, Petkau J, Rao S, Reingold S, Syndulko K, Thompson A, Wallenberg J, Weinshenker B, Willoughby E. Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Ann Neurol*. 1997; 42:379–382. [PubMed: 9307263]
34. Rudick R, Antel J, Confavreux C, Cutter G, Ellison G, Fischer J, Lublin F, Miller A, Petkau J, Rao S, Reingold S, Syndulko K, Thompson A, Wallenberg J, Weinshenker B, Willoughby E. Clinical outcomes assessment in multiple sclerosis. *Ann Neurol*. 1996; 40:469–479. [PubMed: 8797541]
35. Miller DM, Rudick RA, Cutter G, Baier M, Fischer JS. Clinical significance of the multiple sclerosis functional composite: relationship to patient-reported quality of life. *Arch Neurol*. 2000; 57:1319–1324. [PubMed: 10987899]
36. Rudick RA, Cutter G, Reingold S. The multiple sclerosis functional composite: a new clinical outcome measure for multiple sclerosis trials. *Mult Scler*. 2002; 8:359–365. [PubMed: 12356200]
37. Ozakbas S, Ormeci B, Akdede BB, Alptekin K, Idiman E. Utilization of the auditory consonant trigram test to screen for cognitive impairment in patients with multiple sclerosis: comparison with the paced auditory serial addition test. *Mult Scler*. 2004; 10:686–689. [PubMed: 15584495]
38. Rudick RA, Polman CH, Cohen JA, Walton MK, Miller AE, Confavreux C, Lublin FD, Hutchinson M, O'Connor PW, Schwid SR, Balcer LJ, Lynn F, Panzara MA, Sandrock AW. Assessing disability progression with the Multiple Sclerosis Functional Composite. *Mult Scler*. 2009; 15:984–997. [PubMed: 19667023]
39. Ashworth B, Aspinall PA, Mitchell JD. Visual function in multiple sclerosis. *Doc Ophthalmol*. 1989; 73:209–224. [PubMed: 2638240]
40. Bodis-Wollner I, Brannan JR. Hidden visual loss in optic neuropathy is revealed using Gabor patch contrast perimetry. *Clin Neurosci*. 1997; 4:284–291. [PubMed: 9292257]
41. Regan D, Raymond J, Ginsburg AP, Murray TJ. Contrast sensitivity, visual acuity and the discrimination of Snellen letters in multiple sclerosis. *Brain*. 1981; 104:333–350. [PubMed: 7237098]
42. Wender M. Value of Pelli-Robson contrast sensitivity chart for evaluation of visual system in multiple sclerosis patients. *Neurol Neurochir Pol*. 2007; 41:141–143. [PubMed: 17530576]
43. Kupersmith MJ, Seiple WH, Nelson JI, Carr RE. Contrast sensitivity loss in multiple sclerosis. Selectivity by eye, orientation, and spatial frequency measured with the evoked potential. *Invest Ophthalmol Vis Sci*. 1984; 25:632–639. [PubMed: 6724832]
44. Leat SJ, Legge GE, Bullimore MA. What is low vision? A re-evaluation of definitions. *Optom Vis Sci*. 1999; 76:198–211. [PubMed: 10333182]
45. Balcer LJ, Baier ML, Pelak VS, Fox RJ, Shuwairi S, Galetta SL, Cutter GR, Maguire MG. New low-contrast vision charts: reliability and test characteristics in patients with multiple sclerosis. *Mult Scler*. 2000; 6:163–171. [PubMed: 10871827]

46. Balcer LJ, Frohman EM. Evaluating loss of visual function in multiple sclerosis as measured by low-contrast letter acuity. *Neurology*. 2010; 74(Suppl 3):S16–S23. [PubMed: 20421569]
47. Talman LS, Bisker ER, Sackel DJ, Long DA Jr, Galetta KM, Ratchford JN, Lile DJ, Farrell SK, Loguidice MJ, Remington G, Conger A, Frohman TC, Jacobs DA, Markowitz CE, Cutter GR, Ying GS, Dai Y, Maguire MG, Galetta SL, Frohman EM, Calabresi PA, Balcer LJ. Longitudinal study of vision and retinal nerve fiber layer thickness in multiple sclerosis. *Ann Neurol*. 2010; 67:749–760. [PubMed: 20517936]
48. Rosser DA, Cousens SN, Murdoch IE, Fitzke FW, Laidlaw DA. How sensitive to clinical change are ETDRS and logMAR visual acuity measurements? *Invest Ophthalmol Vis Sci*. 2003; 44:3278–3281. [PubMed: 12882770]
49. Ma SL, Shea JA, Galetta SL, Jacobs DA, Markowitz CE, Maguire MG, Balcer LJ. Self-reported visual dysfunction in multiple sclerosis: new data from the VFQ-25 and development of an MS-specific vision questionnaire. *Am J Ophthalmol*. 2002; 133:686–692. [PubMed: 11992867]
50. Raphael BA, Galetta KM, Jacobs DA, Markowitz CE, Liu GT, Nano-Schiavi ML, Galetta SL, Maguire MG, Mangione CM, Globe DR, Balcer LJ. Validation and test characteristics of a 10-item neuro-ophthalmic supplement to the NEI-VFQ-25. *Am J Ophthalmol*. 2006; 142:1026–1035. [PubMed: 17046704]
51. Mowry EM, Loguidice MJ, Daniels AB, Jacobs DA, Markowitz CE, Galetta SL, Nano-Schiavi ML, Cutter GR, Maguire MG, Balcer LJ. Vision related quality of life in multiple sclerosis: correlation with new measures of low and high contrast letter acuity. *J Neurol Neurosurg Psychiatry*. 2009; 80:767–772. [PubMed: 19240050]
52. Submacular Surgery Trials Research Group. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) SST Report Number 19. *Ophthalmic Epidemiol*. 2007; 14:205–215. [PubMed: 17896299]
53. Submacular Surgery Trials Research Group. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization—SST Report Number 1. *Arch Ophthalmol*. 2003; 121:531–539. [PubMed: 12695250]
54. McKean-Cowdin R, Varma R, Wu J, Hays RD, Azen SP. Los Angeles Latino Eye Study Group. Severity of visual field loss and health-related quality of life. *Am J Ophthalmol*. 2007; 143:1013–1023. [PubMed: 17399676]
55. Globe DR, Wu J, Azen SP, Varma R. Los Angeles Latino Eye Study Group. The impact of visual impairment on self-reported visual functioning in Latinos: The Los Angeles Latino Eye Study. *Ophthalmology*. 2004; 111:1141–1149. [PubMed: 15177964]
56. Pineles SL, Birch EE, Talman LS, Sackel DJ, Frohman EM, Calabresi PA, Galetta SL, Maguire MG, Balcer LJ. One eye or two: a comparison of binocular and monocular low-contrast acuity testing in multiple sclerosis. *Am J Ophthalmol*. 2011; 152:133–140. [PubMed: 21570055]
57. Newman NJ, Wolfe JM, Stewart MI, Lessell S. Binocular visual function in patients with a history of monocular optic neuritis. *Clin Vision Sci*. 1991; 6:95–107.
58. Wu GF, Schwartz ED, Lei T, Souza A, Mishra S, Jacobs DA, Markowitz CE, Galetta SL, Nano-Schiavi ML, Desiderio LM, Cutter GR, Calabresi PA, Udupa JK, Balcer LJ. Relation of vision to global and regional brain MRI in multiple sclerosis. *Neurology*. 2007; 69:2128–2135. [PubMed: 17881718]
59. Kolappan M, Henderson AP, Jenkins TM, Wheeler-Kingshott CA, Plant GT, Thompson AJ, Miller DH. Assessing structure and function of the afferent visual pathway in multiple sclerosis and associated optic neuritis. *J Neurol*. 2009; 256:305–319. [PubMed: 19296047]
60. Halliday AM, McDonald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. *Br Med J*. 1973; 4:661–664. [PubMed: 4758547]
61. Thurtell MJ, Bala E, Yaniglos SS, Rucker JC, Peachey NS, Leigh RJ. Evaluation of optic neuropathy in multiple sclerosis using low-contrast visual evoked potentials. *Neurology*. 2009; 73:1849–1857. [PubMed: 19949031]
62. Laron M, Cheng H, Zhang B, Schiffman JS, Tang RA, Frishman LJ. Assessing visual pathway function in multiple sclerosis patients with multifocal visual evoked potentials. *Mult Scler*. 2009; 15:1431–1441. [PubMed: 19995841]

63. Naismith RT, Tutlam NT, Xu J, Shepherd JB, Klawiter EC, Song SK, Cross AH. Optical coherence tomography is less sensitive than visual evoked potentials in optic neuritis. *Neurology*. 2009; 73:46–52. [PubMed: 19564583]
64. Sepulcre J, Goñi J, Masdeu JC, Bejarano B, Vélez de Mendizábal N, Toledo JB, Villoslada P. Contribution of white matter lesions to gray matter atrophy in multiple sclerosis: evidence from voxel-based analysis of T1 lesions in the visual pathway. *Arch Neurol*. 2009; 66:173–179. [PubMed: 19204153]
65. Ikuta F, Zimmerman HM. Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. *Neurology*. 1976; 26:26–28. [PubMed: 944889]
66. Toussaint D, Périer O, Verstappen A, Bervoets S. Clinicopathological study of the visual pathways, eyes, and cerebral hemispheres in 32 cases of disseminated sclerosis. *J Clin Neuro-Ophthalmol*. 1983; 3:211–220.
67. Sisto D, Trojano M, Vetrugno M, Trabucco T, Iliceto G, Sborgia C. Subclinical visual involvement in multiple sclerosis: a study by MRI, VEPs, frequency-doubling perimetry, standard perimetry, and contrast sensitivity. *Invest Ophthalmol Vis Sci*. 2005; 46:1264–1268. [PubMed: 15790888]
68. Lycke J, Tolleson PO, Frisén L. Asymptomatic visual loss in multiple sclerosis. *J Neurol*. 2001; 248:1079–1086. [PubMed: 12013586]
69. Engell T, Trojaborg W, Raun NE. Subclinical optic neuropathy in multiple sclerosis. A neuro-ophthalmological investigation by means of visually evoked response, Farnworth-Munsell 100 Hue test and Ishihara test and their diagnostic value. *Acta Ophthalmol (Copenh)*. 1987; 65:735–740. [PubMed: 3434241]
70. Cheng H, Laron M, Schiffman JS, Tang RA, Frishman LJ. The relationship between visual field and retinal nerve fiber layer measurements in patients with multiple sclerosis. *Invest Ophthalmol Vis Sci*. 2007; 48:5798–5805. [PubMed: 18055834]
71. Pulicken M, Gordon-Lipkin E, Balcer LJ, Frohman E, Cutter G, Calabresi PA. Optical coherence tomography and disease subtype in multiple sclerosis. *Neurology*. 2007; 69:2085–2092. [PubMed: 18040015]
72. Costello F, Hodge W, Pan YI, Freedman M, DeMeulemeester C. Differences in retinal nerve fiber layer atrophy between multiple sclerosis subtypes. *J Neurol Sci*. 2009; 281:74–79. [PubMed: 19303605]
73. Henderson AP, Trip SA, Schlottmann PG, Altmann DR, Garway-Heath DF, Plant GT, Miller DH. An investigation of the retinal nerve fibre layer in progressive multiple sclerosis using optical coherence tomography. *Brain*. 2008; 131:277–287. [PubMed: 18056739]
74. Gordon-Lipkin E, Chodkowski B, Reich DS, Smith SA, Pulicken M, Balcer LJ, Frohman EM, Cutter G, Calabresi PA. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. *Neurology*. 2007; 69:1603–1609. [PubMed: 17938370]
75. Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, García-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. *Neurology*. 2007; 68:1488–1494. [PubMed: 17470751]
76. Cettomai D, Pulicken M, Gordon-Lipkin E, Salter A, Frohman TC, Conger A, Zhang X, Cutter G, Balcer LJ, Frohman EM, Calabresi PA. Reproducibility of optical coherence tomography in multiple sclerosis. *Arch Neurol*. 2008; 65:1218–1222. [PubMed: 18779426]
77. Zaveri MS, Conger A, Salter A, Frohman TC, Galetta SL, Markowitz CE, Jacobs DA, Cutter GR, Ying GS, Maguire MG, Calabresi PA, Balcer LJ, Frohman EM. Retinal imaging by laser polarimetry and optical coherence tomography evidence of axonal degeneration in multiple sclerosis. *Arch Neurol*. 2008; 65:924–928. [PubMed: 18625859]
78. Salter AR, Conger A, Frohman TC, Zivadinov R, Eggenberger E, Calabresi P, Cutter G, Balcer L, Frohman EM. Retinal architecture predicts pupillary reflex metrics in MS. *Mult Scler*. 2008; 15:479–486. [PubMed: 19091882]
79. Pueyo V, Ara JR, Almarcegui C, Martin J, Güerri N, García E, Pablo LE, Honrubia FM, Fernandez FJ. Sub-clinical atrophy of the retinal nerve fibre layer in multiple sclerosis. *Acta Ophthalmol*. 2009 [Epub ahead of print].
80. Costello F, Hodge W, Pan YI, Metz L, Kardon RH. Retinal nerve fiber layer and future risk of multiple sclerosis. *Can J Neurol Sci*. 2008; 35:482–487. [PubMed: 18973066]

81. Burkholder BM, Osborne B, Loguidice MJ, Bisker E, Frohman TC, Conger A, Ratchford JN, Warner C, Markowitz CE, Jacobs DA, Galetta SL, Cutter GR, Maguire MG, Calabresi PA, Balcer LJ, Frohman EM. Macular volume determined by optical coherence tomography as a measure of neuronal loss in multiple sclerosis. *Arch Neurol*. 2009; 66:1366–1372. [PubMed: 19901168]
82. Syc SB, Warner CV, Hiremath GS, Farrell SK, Ratchford JN, Conger A, Frohman T, Cutter G, Balcer LJ, Frohman EM, Calabresi PA. Reproducibility of high-resolution optical coherence tomography in multiple sclerosis. *Mult Scler*. 2010 [Epub ahead of print].
83. Kanamori A, Escano MF, Eno A, Nakamura M, Maeda H, Seya R, Ishibashi K, Negi A. Evaluation of the effect of aging on retinal nerve fiber layer thickness measured by optical coherence tomography. *Ophthalmologica*. 2003; 217:273–278.
84. Henderson APD, Altmann DR, Trip AS, Kallis C, Jones SJ, Schlottmann PG, Garway-Heath DF, Plant GT, Miller DH. A serial study of retinal changes following optic neuritis with sample size estimates for acute neuroprotection trials. *Brain*. 2010; 133:2592–2602. [PubMed: 20566483]
85. Costello F, Hodge W, Pan YI, Eggenberger E, Freedman MS. Using retinal architecture to help characterize multiple sclerosis patients. *Can J Ophthalmol*. 2010; 45(5):520–526. [PubMed: 20838421]
86. Bock M, Brandt AU, Kuchenbecker J, Dörr J, Pfueller CF, Weinges-Evers N, Gaede G, Zimmermann H, Bellmann-Strobl J, Ohlraun S, Zipp F, Paul F. Impairment of contrast visual acuity as a functional correlate of retinal nerve fibre layer thinning and total macular volume reduction in multiple sclerosis. *Br J Ophthalmol*. 2011 [Epub ahead of print].
87. Merle H, Olindo S, Donnio A, Beral L, Richer R, Smadja D, Cabre P. Retinal nerve fiber layer thickness and spatial and temporal contrast sensitivity in multiple sclerosis. *Eur J Ophthalmol*. 2010; 20:158–166. [PubMed: 19882537]
88. Galetta KM, Graves J, Talman LS, Lile DJ, Frohman EM, Calabresi PA, Galetta SL, Balcer LJ. Visual pathway loss in benign Multiple Sclerosis: a longitudinal study. [unpublished data].
89. Shiee N, Bazin PL, Ozturk A, Reich DS, Calabresi PA, Pham DL. A topology-preserving approach to the segmentation of brain images with multiple sclerosis lesions. *NeuroImage*. 2010; 49:1524–1535. [PubMed: 19766196]
90. Filippi M, Rocca MA, Calabrese M, Sormani MP, Rinaldi F, Perini P, Comi G, Gallo P. Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. *Neurology*. 2010; 75:1988–1994. [PubMed: 21115953]
91. Pitt D, Boster A, Pei W, Wohleb E, Jasne A, Zachariah CR, Rammohan K, Knopp MV, Schmalbrock P. Imaging cortical lesions in multiple sclerosis with ultra-high-field magnetic resonance imaging. *Arch Neurol*. 2010; 67:812–818. [PubMed: 20625086]
92. Watson GM, Keltner JL, Chin EK, Harvey D, Nguyen A, Park SS. Comparison of retinal nerve fiber layer and central macular thickness measurements among five different optical coherence tomography instruments in patients with multiple sclerosis and optic neuritis. *J Neuro-Ophthalmol*. 2011; 31:110–116.
93. Garcia-Martin E, Pinilla I, Idoipe M, Fuertes I, Pueyo V. Intra and inter-operator reproducibility of retinal nerve fiber and macular thickness measurements using Cirrus Fourier-domain OCT. *Acta Ophthalmol*. 2011; 89:e23–e29. [PubMed: 21106044]
94. Sull AC, Vuong LN, Price LL, Srinivasan VJ, Gorczynska I, Fujimoto JG, Schuman JS, Duker JS. Comparison of spectral domain optical coherence tomography instruments for assessment of normal macular thickness. *Retina*. 2010; 30:235–245. [PubMed: 19952997]
95. Wollstein G, Kagemann L, Bilonick RA, Ishikawa H, Folio LS, Gabriele ML, Ungar AK, Duker JS, Fujimoto JG, Schuman JS. Retinal nerve fibre layer and visual function loss in glaucoma: the tipping point. *Br J Ophthalmol*. 2011 [epub ahead of print].
96. Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrell SK, Oakley JD, Durbin MK, Meyer SA, Balcer LJ, Frohman EM, Rosenzweig JM, Newsome SD, Ratchford JN, Nguyen QD, Calabresi PA. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. *Brain*. 2011 advance access 16pp.
97. Davies EC, Galetta KM, Sackel DJ, Talman LS, Frohman EM, Calabresi PA, Galetta SL, Balcer LJ. Retinal ganglion cell layer volumetric assessment by spectral-domain optical coherence

- tomography in multiple sclerosis: application of a high-precision manual estimation technique. *J Neuro-Ophthalmol.* 2011; 31:260–264.
98. Tan O, Li G, Lu AT, Varma R, Huang D. Advanced Imaging for Glaucoma Study Group. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. *Ophthalmology.* 2008; 115:949–956. [PubMed: 17981334]
 99. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, Varma R, Huang D. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. *Ophthalmology.* 2009; 116:2305–2314. [PubMed: 19744726]
 100. Ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2005; 46:2012–2017. [PubMed: 15914617]
 101. Green A, McQuaid S, Hauser SL, Allen IV, Lyness R. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. *Brain.* 2010; 133:1591–1601. [PubMed: 20410146]
 102. Shindler KS, Ventura E, Dutt M, Elliott P, Fitzgerald DC, Rostami A. Oral resveratrol reduces neuronal damage in a model of multiple sclerosis. *J Neuro-Ophthalmol.* 2010; 30:328–339.
 103. Walter SD, Ishikawa H, Galetta KM, Sakai RE, Feller DJ, Wilson JA, Maguire MG, Galetta SL, Frohman E, Calabresi PA, Schuman JS, Balcer LJ. Ganglion cell loss in relation to visual disability in multiple sclerosis. [unpublished data].
 104. Keltner JL, Cello KE, Balcer LJ, Calabresi PA, Markowitz CE, Werner JS. Stratus OCT quality control in two multi-centre Multiple Sclerosis clinical trials. *J Neuro-Ophthalmol.* 2011; 35:57–64.
 105. Werner JS, Keltner JL, Zawadzki RJ, Choi SS. Outer retinal abnormalities associated with inner retinal pathology in nonglaucomatous and glaucomatous optic neuropathies. *Eye.* 2011; 25:279–289. [PubMed: 21293495]

FIG. 1.

Low-contrast letter acuity chart (low-contrast Sloan letter chart, Precision Vision, LaSalle, IL).

* These charts have a standardized format based on Early Treatment Diabetic Retinopathy Study visual acuity charts, the standard used in ophthalmology clinical trials, and have several advantages over standard Snellen charts or near vision testing cards as traditionally used in MS trials: 1) letters (Sloan letters) are designed to be equally detectable for normal observers; 2) each line has an equal number of letters (five per line); 3) spacing between letters and lines is proportional to the letter size; 4) change in visual acuity from one line to another occurs in equal logarithmic steps (change of three lines constitutes a doubling of the visual angle); 5) visual acuity (for high-contrast [black letters on white] chart) may be specified by Snellen notation for descriptive purposes (i.e., 20/20), by the number of letters

identified correctly. This figure shows the 25% contrast level for purposes of illustrating format; the actual contrast levels used in these trials, 2.5% and 1.25%, have substantially lighter gray letters. The charts measure 14×14 inches for easy use and portability in the MS clinical trial setting; charts may also be mounted on a retroilluminated cabinet, thus eliminating the need for standardization of room lighting levels.

Reprinted with permission from Balcer LJ, et al. *Neurology*. 2007;68:1299–1304.

FIG. 2.

Logistic regression analyses demonstrating capacity for each visual function test to predict multiple sclerosis (MS) vs disease-free control status in a heterogeneous MS cohort, accounting simultaneously for age. Odds ratios in favor of participants with worse vision scores being MS patients (vs disease-free controls) were greatest for low-contrast letter acuity (Sloan charts) and contrast sensitivity (Pelli–Robson chart). These measures thus best distinguish MS patients from disease-free control subjects, even after accounting for age differences between the two groups. VF = visual field.

Reprinted with permission from Balcer LJ, et al. *Neurology*. 2003;61:1367–1373.

FIG. 3.

Scatter plots showing relation of low-contrast letter acuity to retinal nerve fiber layer (RNFL) thickness in microns for eyes from a heterogeneous MS cohort ($n=82$) with a history of acute optic neuritis (ON). The left panel shows eyes with abnormal low-contrast acuity scores, defined as 7 letters below the mean of a disease-free control group. Eyes in the right panel have normal low-contrast acuity at 2.5% contrast. Among eyes with abnormal low-contrast acuity, worse scores were significantly associated with lower (thinner) peripapillary RNFL, accounting for age and adjusting for within-patient, inter-eye correlations.

FIG. 4.

Single frame of a macular spectral-domain OCT image with retinal layers labeled and the GCL outlined in red as segmented manually for the GCL volume analysis. From Davies EC, et al. *J Neuro-Ophthalmol.* 2011;31:260–264. Labeling adapted from Werner JS, et al. *Eye.* 2011;25:279–289.

TABLE 1
Mean reference values from recent investigations of vision, QOL, and OCT in MS

	Disease-Free Controls	All MS	MS, No History of ON	MS, History of ON	References for Data *
High-contrast visual acuity (VA), ETDRS, number of letters correct	64 ± 5 (n=61 eyes)	59 ± 8 (n=239 eyes)	60 ± 6 (n=150 eyes)	58 ± 9 (n=87 eyes)	103 * (22,47,56,81,84)
<i>Binocular testing</i>	66 ± 5 (n=324 pts)	62 ± 8 (n=1,007 pts)	63 ± 7 (n=544 pts)	61 ± 10 (n=463 pts)	56 * (7-10,51)
Low-contrast letter acuity (2.5%), number of letters correct	34 ± 8 (n=61 eyes)	26 ± 11 (n=239 eyes)	28 ± 9 (n=150 eyes)	22 ± 12 (n=87 eyes)	103 * (22,47,56)
<i>Binocular testing</i>	43 ± 6 (n=324 pts)	36 ± 10 (n=1,007 pts)	38 ± 9 (n=544 pts)	35 ± 11 (n=463 pts)	56 * (7-10,51)
Low-contrast letter acuity (1.25%), number of letters correct	25 ± 7 (n=61 eyes)	16 ± 10 (n=239 eyes)	18 ± 10 (n=150 eyes)	11 ± 11 (n=87 eyes)	103 * (22,47,56,81,84)
<i>Binocular testing</i>	34 ± 8 (n=324 pts)	24 ± 11 (n=1,007 pts)	26 ± 11 (n=544 pts)	22 ± 12 (n=463 pts)	56 * (7-10,51)
NEI-VFQ-25 composite score, best score=100	96 ± 4 (n=31 pts)	88 ± 13 (n=122 pts)	90 ± 12 (n=111 pts)	85 ± 14 (n=51 pts)	103 * (49-51,56)
10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25, best score=100	97 ± 3 (n=31 pts)	87 ± 13 (n=122 pts)	88 ± 12 (n=111 pts)	83 ± 14 (n=51 pts)	103 * (49-51,56)
<i>Time-domain (TD) OCT</i>					
Peripapillary RNFL thickness, µm	104.5 ± 10.7 (n=219 eyes)	92.5 ± 16.7 (n=1,058 eyes)	95.6 ± 14.5 (n=730 eyes)	85.7 ± 19.0 (n=328 eyes)	81 * (20-22,47,70-84)
Total macular volume, mm ³	6.84 ± 0.36 (n=219 eyes)	6.54 ± 0.51 (n=1,058 eyes)	6.63 ± 0.48 (n=730 eyes)	6.36 ± 0.53 (n=328 eyes)	81 * (20-22,70-84)
<i>Spectral-domain (SD) OCT</i>					
Peripapillary RNFL thickness, µm	92.9 ± 10.0 (n=61 eyes)	84.3 ± 12.8 (n=239 eyes)	87.6 ± 11.1 (n=150 eyes)	78.4 ± 13.6 (n=87 eyes)	103 * (96,105)

	Disease-Free Controls	All MS	MS, No History of ON	MS, History of ON	References for Data *
Ganglion cell + inner plexiform layer (GCL+IPL), μm	88.9 $\pm$ 6.9 (n=61 eyes)	84.1 $\pm$ 8.4 (n=239 eyes)	87.0 $\pm$ 6.6 (n=150 eyes)	79.7 $\pm$ 9.2 (n=87 eyes)	103 * (96,105)
Macular RNFL, μm	29.6 $\pm$ 6.0 (n=61 eyes)	23.5 $\pm$ 8.2 (n=239 eyes)	25.5 $\pm$ 7.1 (n=150 eyes)	20.0 $\pm$ 9.0 (n=87 eyes)	103 * (96,105)

Abbreviations: MS = multiple sclerosis; ETDRS = Early Treatment Diabetic Retinopathy Study; QOL = quality of life ; NEI-VFQ-25 = 25-Item National Eye Institute Visual Functioning Questionnaire; TD = time-domain (OCT-3 platform); SD = spectral-domain (Cirrus platform); OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

* Reference with asterisk is source of data presented in table; references that contain similar data are in parentheses.